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Review

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Bartter syndrome: an overview

I. AMIRLAK and K.P. DAWSON

From the Department of Paediatrics, Faculty of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

Summary

The term Bartter syndrome denotes a group of renal diseases which share a common denominator of hypokalaemia and metabolic alkalosis. The patch-clamp technique has made possible the analysis of single ion channels, improving our understanding of the molecular physiopathology of all the 'Bartter-like' syndromes. Genetic mapping of each defect has further clarified the mutations involved and the possible modes of inheritance. This improved understanding has opened new avenues for therapy, improving mortality and morbidity in these patients. Another group of illnesses, the 'pseudo-Bartter syndrome', may produce a hypokalaemic metabolic alkalosis without primary renal disease. The underlying illness needs to be identified and treated.

Introduction

In 1962, Frederic Bartter and his colleagues wrote their seminal paper[1] based on two patients with hypokalaemic metabolic alkalosis, hyperaldosteronism, normal blood pressure, decreased pressor responsiveness to angiotensin II infusion and hyperplasia of the juxtaglomerular apparatus. Subsequently, a wide variety of hypokalaemic metabolic alkalotic states, with different clinical and laboratory findings as well as age-related presentations, have been reported, leading to confusing variations in nomenclature. Terms such as Bartter-like syndrome do little to help the clinician identify the specific metabolic defect and treat the patient's illness correctly. It may be better to sub-classify Bartter syndrome by renal pathophysiological abnormality. By this method, Bartter syndrome falls into four subgroups: (i) antenatal Bartter syndrome (hyperprostaglandin E2 syndrome); (ii) the Gitleman variety of Bartter syndrome (Gitleman syndrome); (iii) classical Bartter syndrome; and (iv) pseudo-Bartter syndrome. We address the clinical and pathological aspects, and the genetics, of each of the above in detail, hoping to clarify the path to early diagnosis and appropriate treatment.

Antenatal Bartter syndrome (hyperprostaglandin E2 syndrome)

The signs and symptoms of antenatal Bartter Syndrome may be present and identifiable *in utero*.[2,5,9,11,14,22] Unexplained polyhydramnios between 24 and 36 weeks of gestation is a well-documented early sign of this syndrome according to most investigators.[2,14,51] Another important finding at this stage is biochemical abnormality of the amniotic fluid, with normal sodium, potassium and prostaglandin levels, but consistently elevated chloride levels.[2–5] The infants are usually born prematurely.[2,30] After birth, the most important clinical

Address correspondence to Dr I. Amirlak, Department of Paediatrics, Faculty of Medicine and Health Sciences, UAE University, PO Box 17666, Al Ain, United Arab Emirates. e-mail: iradj.amirlak@uaeu.ac.ae

finding is hyposthenuria (urine of low specific gravity) and rapid weight loss.[2,5] Lethargy and poor feeding often develop. In the first week of life, laboratory investigation shows a metabolic alkalosis associated with hypokalaemia. The urine has low specific gravity with very high sodium, chloride and calcium levels, while potassium is normal.[2] However, after 1–3 weeks, the level of potassium in the urine rises to considerably above normal, with relatively less sodium than in the first week of life.[2] Prostaglandin levels are high, both in blood and in urine.[2,8–10] Hyperprostaglandin E2 is a secondary phenomenon due to fluid and electrolyte loss, and will be suppressed by appropriate fluid and electrolyte replacement over a period of time.[2] Therefore, calling this entity hyperprostaglandin E2 syndrome[8] rather than antenatal Bartter syndrome seems inappropriate, since the hyperprostaglandism is secondary to the basic pathology.[2,23] Levels of renin and aldosterone are also very high, and important in establishing the diagnosis.[2,10–12] Untreated infants will fail to thrive, and may die in a few days as a result of dehydration, poor feeding and/or severe electrolyte disturbance. Mild mental retardation has been observed in some children with this disease; however, we have not encountered such retardation in our infant patients who were diagnosed and treated early, and the putative brain insult may therefore be linked to delay in diagnosis and treatment. There are also reports of special facial features, such as a triangular face characterized by prominent forehead, large eyes, protruding ears and drooping mouth.[16,17,31] Strabismus may also be present.[17] There are now reports of sensorineural deafness in a Bedouin family[16] and also in one from Costa Rica.[17]

Pathophysiology of antenatal Bartter syndrome

The pathophysiology of antenatal Bartter syndrome can only be explained if one first looks at the renal handling of sodium, potassium and chloride at the nephron level. Filtration of electrolytes in the glomeruli is complete: the concentration of Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+} (ionized calcium comprising 60% of total serum Ca) and other electrolytes in the Bowman's capsule is the same as in whole blood.[18,19] At the level of the proximal tubule, 67% of filtered Na^+ and K^+ is reabsorbed, while at the level of the thick ascending limb of loop of Henle, 20% of filtered Na^+ and K^+ is reabsorbed. Reabsorption of Cl^- in this segment is closely related to that of K^+ and Na^+. The proximal tubule and thick ascending limb of loop of Henle reabsorb 90% of filtered Ca^{2+}. Reabsorption of Ca^{2+} is a passive process and is coupled to Na^+ reabsorption. Any defect in the normal function of the thick ascending loop of Henle is relevant to Na^+, K^+, and Cl^-, and will impair their absorption. This will have a secondary effect on the osmolality of the peritubular space and subsequently reduce the movement of water from the descending limb of the loop of Henle in the direction of the tubular space to the interstitium. The final result of such a phenomena is the flooding of the distal tubule with diluted urine with a high content of Na^+, K^+, Cl^- and Ca^{2+}.

In the thick ascending loop of Henle, Na^+-K^+-$2Cl^-$ (site 1, Figure 1) in the form of an electroneutral cotransport passes through the apical membrane of the tubule into the tubular cell.[19–21] At the basolateral cell membrane are the Na^+-K^+ pumps which, when active, pump sodium out of the cell into the interstitium and then the blood, and potassium from the interstitium into the cell.[27–29] The function of these pumps is an active process using ATP, and they are thus called Na^+-K^+ ATPase pumps

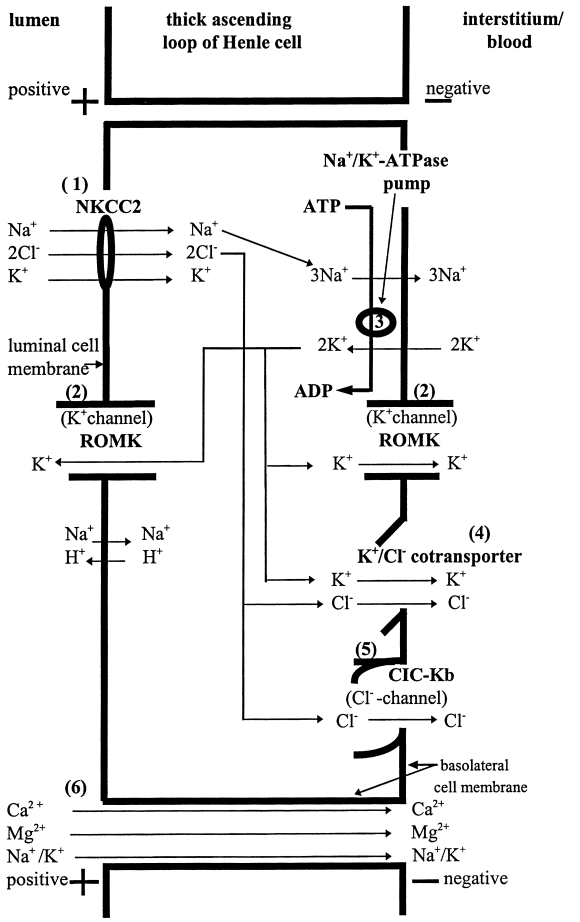

Figure 1. Transport sites in the thick ascending limb of the loop of Henle. (1) Electroneutral Na^+,K^+,$2Cl^-$ cotransport in the apical membrane. (2) K^+ channel (Rat outer medulla potassium channel) in the apical and the basolateral cell membrane. (3) Na^+/K^+-ATPase pump in the basolateral cell membrane. (4) K^+/Cl^- cotransporter in the basolateral cell membrane. (5) Cl^-channel (ClC-Kb) in the basolateral cell membrane. (6) Intercellular space.

(site 3, Figure 1). Intracellular K^+ needs to move out of the cell to the blood as well as into the luminar space. Movement of potassium into the luminar space is of the utmost importance for the process of reabsorption of 20% of the filtered Na (140 meq/l) which takes place in this segment of the loop of Henle. Each molecule of Na^+ requires one molecule of K^+ in the electroneutral passage through the luminal membrane in the form of Na^+-K^+-$2Cl^-$. Only 20% of filtered K^+ (5 meq/1) is reabsorbed in the thick ascending loop of Henle. This will not provide the necessary K^+ ions[4,25,26] for reabsorption of sodium. The passage and movement of K^+ ions takes place through channels known as K^+ channels (site 2, Figure 1) or ROMK (rat outer medulla K^+ channel). Their opening and closure are under the control of the Ca^{2+} content of the cell and its ATP level. When the Na^+-K^+ ATPase pump (site 3, Figure 1) becomes active, cell ATP falls, and this opens the potassium channels, facilitating movement of K^+ from the intracellular space to the lumen as well as into the interstitium. Movement of K^+ from the intracellular space into the intraluminal space provides the potassium molecules necessary for Na^+-K^+-$2Cl^-$ cotransport and subsequent absorption of Na^+ and Cl^- from the luminal space of the thick ascending loop of Henle. Thus recirculation of K^+ through the potassium channels facilitates electroneutral movement of Na^+-K^+-$2Cl^-$ through the apical cell membrane. Positive potential of the lumen also acts as a driving force for the passage of K^+ and Na^+ through the paracellular pathways (intercellular spaces) into the blood (site 6, Figure 1). Calcium and magnesium also pass through these paracellular spaces (site 6, Figure 1). Passage of Cl^- from the cell into the interstitium can take place through kidney-specific chloride channels (ClC-Kb) (site 5, Figure 1), and via K^+/Cl^- cotransport system (site 4, Figure 1). In the apical membrane, there is also an exchange of Na^+/H^+. This is summarized schematically in Figure 1.

Thus the handling of chloride ions by the thick ascending loop of Henle is an intimate part of the normal function of Na^+-K^+-$2Cl^-$ electroneutral cotransport, as well as K^+ channels (ROMK) and Cl^- channels (ClC-Kb). In other words, defects in Cl^- transport may result from any loss or altered function of Na^+-K^+-$2Cl^-$ cotransporter and/or K^+ channels, as well as chloride channels. However, no defect in chloride channels has been identified which relates to the pathogenesis of antenatal Bartter syndrome. The long-term use of loop diuretics such as frusemide produces electrolyte blood and urine changes resembling those of antenatal Bartter syndrome,[33,34,38,46] and this is an example of altered function. Loss of function can result from mutations in any of the genes encoding either the Na^+-K^+-$2Cl^-$ cotransporter or K^+ channels. The locus of the gene responsible for Na^+-K^+-$2Cl^-$ cotransport (*NKCC2*) in apical cell membranes (site 1, Figure 1) has been identified by Simon *et al*. in 1996 on chromosome 15q15-21.[37] Six independent mutations were identified in their patients with antenatal Bartter syndrome.

Genetic study of another group of patients with antenatal Bartter syndrome with a normal gene for Na^+-K^+-$2Cl^-$ cotransport revealed a mutation in the gene involving K^+ channels.[39–41] The locus of the gene responsible for these inwardly rectifying K^+ channels (*ROMK*) (site 2, Figure 1) was identified in chromosome 11q24-25.[40,41] Here again eleven independent mutations were mapped, indicating genetic heterogenicity.[39] Study of familial cases of antenatal Bartter syndrome revealed a definite autosomal recessive pattern.

Defects in either Na^+-K^+-$2Cl^-$ cotransport or K^+ channels will result in malreabsorption of Na^+, K^+, Cl^-, and Ca^{2+} in the thick ascending limb of loop of Henle primarily, with subsequent reabsorption of H_2O in the descending loop of Henle. The result of such a defect will be the delivery of large volumes of urine with a high content of Na^+, K^+, Cl^- and Ca^{2+} to the distal tubule. In the distal tubule, part of the delivered Na^+ will be reabsorbed in exchange for intracellular K^+. By this action, partial but incomplete concentration of the intraluminal fluid will be accomplished, while more potassium wasting becomes evident. However, this impaired sodium absorption in the thick ascending limp of loop of Henle will result in increased levels of prostaglandin E2.[38,89,91] This interrelation has been documented in normal individuals using loop diuretics.[38] Increased prostaglandin E2 levels will exacerbate the primary defect of chloride transport in the thick ascending loop of Henle which will: (i) stimulate the renin-angiotensin-aldosterone axis causing hypokalemia due to increased aldosterone activity; (ii) impede ROMK channel activity and hence decrease NaCl transport; and (iii) impede H_2O reabsorption in the collecting ducts due to a secondary effect on vasopressin activity, resulting in hyposthenuria.

Volume contraction will activate the renin-aldosterone axis. This can be seen by the high levels of both renin and aldosterone in both blood and urine of patients with antenatal Bartter syndrome. The action of aldosterone in the distal tubule is twofold. First, the increased movement of Na^+ from the luminal space intracellularly in exchange for intracellular K^+ via the principal cells of the late distal tubule and the collecting duct, hence enhancing potassium wasting. This is accomplished by increasing the activity of the Na^+-K^+ ATPase pumps at the basolateral cell membrane (site 3, Figure 1), which pump Na^+ out of the tubular cell into interstitium and K^+ into the cell from the interstitium. This increases intracellular K^+, creating more of a

K^+ concentration gradient with respect to the lumen, and henceforth more loss of K^+ into the lumen through the apical membrane and finally into the urine. Secondly, aldosterone stimulates the intercalated cells of the late distal tubule and collecting duct to exchange intracellular H^+ for intraluminal K^+, with subsequent exaggeration of the metabolic alkalosis due to H^+ loss.

The next question to be answered is why these patients, who have high levels of renin and angiotensin, do not develop high blood pressure? Could this be due to non-responsiveness of their blood vessels to angiotensin as suggested by Bartter (end-organ failure)? It has now been demonstrated that patients with Bartter syndrome will show a normal response to vasopressor agents once their volume is restored to normal.[2]

Another equally important finding in antenatal Bartter syndrome is hypercalciuria. The cause of calcium loss has already been described. Such a continuous loss of calcium results in nephrocalcinosis and secondary renal impairment in many of these patients.[49–51] Indeed, calcium deposits in the kidney of these patients can be picked up by either ultrasonographic examination of the kidneys as early as 2 months[10] or simple abdominal X-ray.

Gitleman syndrome

This phenotype of Bartter syndrome is characterized by a milder course than in the antenatal variety. Onset is late, usually after the age of 20 years. Patients present with fatigue, muscle weakness and recurrent episodes of tetany.[24,53,54,56,57] Biochemically, there is metabolic alkalosis, (serum bicarbonate >29 meq/1) profound hypokalaemia, (serum potassium <3 meq/l; normal >3.5 meq/1) hypomagnesaemia (serum magnesium <0.5 meq/l; normal 0.8–1.0 meq/1) and hypocalciuria, (urinary calcium <2 mg/kg per day; normal 2–7 mg/kg per day).[53–55] Urinary concentrating ability in this disease is mildly impaired.

Pathophysiology of Gitleman syndrome

The basic pathology in this disease is an impaired Na-Cl cotransporter in the distal nephron. Distal tubule and collecting duct together reabsorb about 12% of the filtered Na^+. The early distal tubule, also called the cortical diluting segment, is the site of absorption of NaCl by Na^+-Cl^- cotransport (NCCT) (site 1, Figure 2) and is the site of action of thiazide diuretics.[42,43,55] A similar biochemical abnormality can be seen in long-term use of thiazide diuretics in an otherwise normal individual. NaCl wasting in this part of the distal nephron will lead to mild hypovolaemia, and stimulation of the renin-angiotensin axis.[4] Simon *et al.*[58] showed that there is a complete linkage of Gitleman syndrome to the locus encoding the renal thiazide sensitive Na^+-Cl^- cotransporter on chromosome 16q13, with an autosomal recessive pattern and a 99% penetrance.[67] Mutant alleles in this disease have been reported by Simon and others.[58,66–68] The late distal tubule and collecting duct have two kinds of cells, each with special feature and function. *Principal cells* reabsorb Na^+ and H_2O (site 1, Figure 3) and secrete K^+ (site 2, Figure 3). Aldosterone acts on principal cells to increase Na^+ reabsorption and increase K^+ secretion. *Intercalated cells* secrete H^+ ions in exchange for reabsorption of K^+ ions (site 4, Figure 3). Aldosterone increases H^+ ion secretion by intercalated cells.

Impairment of Na^+-Cl^- cotransport in the early part of the distal tubule results in excessive amounts of Na^+ ion in the late distal tubule. Maximal reabsorption of Na^+ and H_2O and maximal secretion of K^+ ion by the principal cells takes place in this segment.[19,20] At the same time, H^+ is excreted by

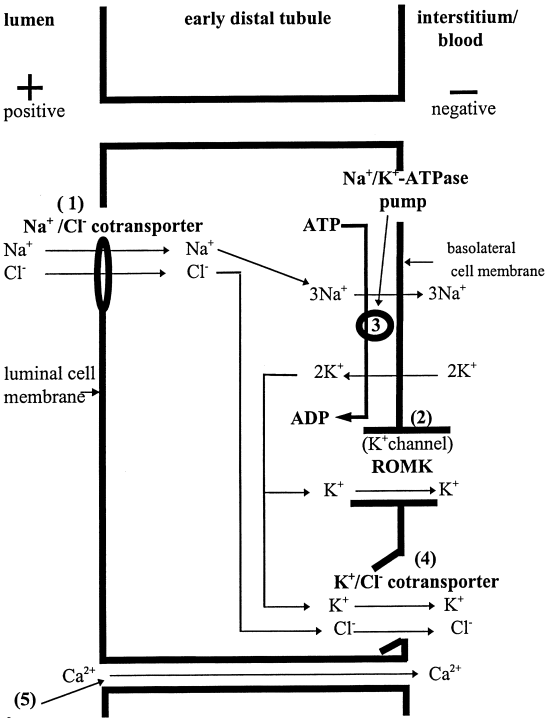

Figure 2. Transport sites in the early distal tubule. (1) Electroneutral Na^+, Cl^- cotransport in the apical membrane. (2) K^+ channel (Rat outer medulla potassium channel) in the apical and the basolateral cell membrane. (3) Na^+/K^+-ATPase pump in the basolateral cell membrane. (4) K^+/Cl^- cotransporter in the basolateral cell membrane. (5) Intercellular space.

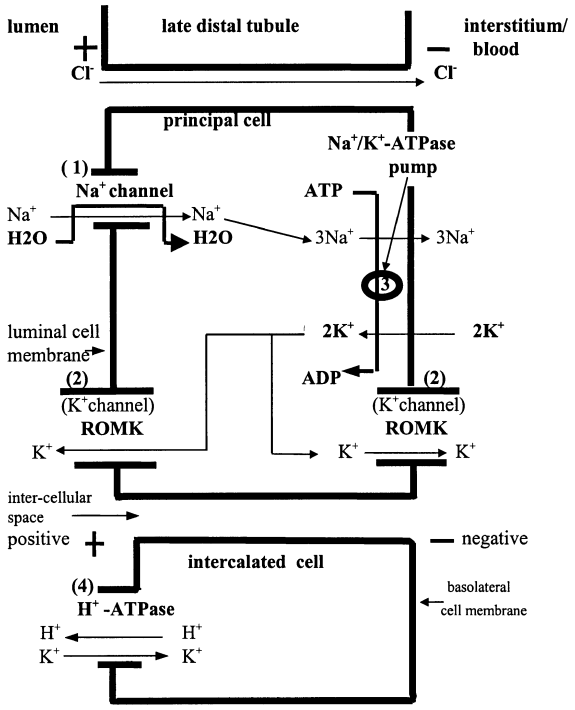

Figure 3. Transport sites in the late distal tubule with two kind of cells. (Principal cell and intercalated cell). (1) Na^+ channel. (2) K^+ channel (Rat outer medulla potassium channel) in the apical and the basolateral cell membrane. (3) Na^+/K^+-ATPase pump in the basolateral cell membrane. (4) Site of K^+/H^+ (H^+-ATPase) exchange in the intercalated cell.

intercalated cells and this, together with impaired Cl^- reabsorption in the early distal tubule, results in metabolic alkalosis. The reason for hypocalciuria, as well as hypomagnesaemia, is not clear. The available literature attributes the high intake of Ca^{2+} in distal tubule and hence hypocalciuria to (a) decreased apical Na^+ uptake driving basolateral Na^+/Ca^{2+} exchange with subsequent increase of Ca^{2+} uptake at the apical membrane level and (b) decreased intracellular Cl^- content increasing the polarity of the apical cell membrane, which stimulates Ca^{2+} uptake.[4,60,61] Hypomagnesaemia in Gitleman syndrome is perhaps due to magnesium wasting in distal convoluted tubules of the nephron due to inhibition of Mg^{2+} uptake in the presence of hypokalaemia.[62–65] It has also been suggested that the metabolic alkalosis may be an important cause of hypomagnesaemia by increasing the resistance of distal tubular cells to Mg^{2+} uptake.[4,63] With low Mg^{2+} levels in the blood, magnesium wasting has been observed in patients with Gitleman syndrome, indicating a too-low renal Mg^{2+} threshold.[4,64]

Classical Bartter syndrome

Classical Bartter syndrome is characterized by early childhood onset. The patients fail to thrive but have no tetany. Symptoms may include polyuria, polydipsia, vomiting, constipation, salt craving, and a tendency to dehydration.[4] Failure to thrive and growth retardation follows if treatment is not initiated. However the normal adult height usually achieved by untreated individuals is due to a delayed adolescent growth spurt. They have hypokalaemic metabolic alkalosis[1] and their urinary Ca^{2+} is either normal or slightly elevated, with the urine concentration being almost normal.

Pathophysiology of classical Bartter syndrome

The biochemical abnormalities of classical Bartter syndrome are all suggestive of a defect related to Cl^- transport in the medullary thick ascending loop of Henle. However, the precise pathway involved is not yet clear. The familial cases of classical Bartter syndrome are inherited as an autosomal recessive entity. A group of patients with this phenotype all had either a large deletion or nonsense, missense, or splice mutations of the gene (*CIC-Kb,* chromosome 1p36) encoding the renal chloride channels of the basolateral cell membrane (site 5, Figure 1).[4,70–74] However, in some patients with classical Bartter syndrome, no abnormality in this gene could be identified. It has therefore been suggested that NaCl transport in the ascending loop of Henle (and the relevant gene/s) may also be involved.[4]

Pseudo-Bartter syndrome

Biochemical abnormalities similar to those found in Bartter syndrome, i.e. hypokalemic metabolic alkalosis, are also encountered in another group of patients with no pathology in the renal tubules. It is therefore very important to identify any other cause that may produce such a metabolic derangement. The list of such conditions includes: cystic fibrosis,[75] surreptitious diuretic use,[34,93] chronic administration of a chloride-deficient diet, bulimia, cyclic vomiting, congenital chloridorrhea, and abuse of laxatives.[4] In all of these conditions, except diuretic use, the chloride content of urine will be low, and this is contrary to all forms of Bartter syndrome. In the case of long use of diuretics, appropriate drug history and demonstration of the diuretic in the urine will establish the diagnosis.[46,72]

Treatment of Bartter syndrome

The therapeutic management of Bartter syndrome is composed of two major aspects: (i) replacement therapy and (ii) use of drugs. With this in mind, the

treatment of each variety of Bartter syndrome will be discussed separately.

Treatment of antenatal Bartter syndrome

The paramount replacement therapy in the immediate neonatal period should be directed towards the correction of fluid and electrolyte imbalance. Fluid loss may surpass 500 ml/kg/day, with very large loss of Na^+ (up to 45 meq/kg/day) and Cl^- in the urine. This will require infusion of large amounts of saline to prevent weight loss and dehydration, and to keep levels of sodium and chloride within the normal range. Due to low urinary potassium loss in the first 2–3 weeks of life, potassium replacement only becomes necessary after this period.[2] Oral replacement therapy with KCI and NaCl in the form of 15% solution, follows the initial intravenous infusion therapy. These oral replacement solutions are given in divided doses three to four times a day. The dose is individually titrated to correct the patient's need.

In terms of medication in antenatal Bartter syndrome, one may be tempted to use potassium-sparing diuretics with the notion of reducing potassium loss. Use of medication, such as spironolactone, helps to improve the overall general condition,[2,45] but will further increase the hypercalciuria and subsequent nephrocalcinosis. There is no long-term experience with other potassium-sparing diuretics such as amiloride. Neutralizing the amplification effect of prostaglandins on the features of Bartter syndrome has long been the main line of drug therapy of this syndrome. Prostaglandin synthetase inhibitors are the main group of drugs recommended in this respect. Among the very many prostaglandin synthetase inhibitors, indomethacin is the most widely used.[2,4,10,79,87] Indomethacin decreases salt wasting and the degree of hypokalaemic alkalosis, and also partially corrects the impaired urine concentrating ability. Indomethacin is known to cause necrotizing enterocolitis in premature infants as well as a severe reduction in glomerular filtration rate.[10,52,59] Decrease of glomerular filtration rate due to use of indomethacin is a reversible process[10] and is dose-dependent. It is therefore recommended that indomethacin should either not be used in premature infants, or its use delayed by perhaps 4–6 weeks after birth. Infants receiving indomethacin should be closely observed for any sign of enterocolitis, and when present, therapy of enterocolitis should be initiated promptly which will include stopping of indomethacin. The recommended dose of indomethacin is 1.5–2.5 mg/kg/day in two or three divided doses.[2] However, higher doses of up to 5 mg/kg/day have also been used, bearing in mind that doses above 3 mg/kg/day are considered nephrotoxic.[2]

An initial dose of 1 mg/kg/day in a week-old infant has been reported to cause renal failure and hyperkalaemia within 3 days with rapid restoration of glomerular function upon discontinuation of indomethacin.[10] A small dose of 0.2 mg/kg/day of indomethacin may be sufficient to keep the salt requirement and diuresis almost within the normal range but with an insufficient effect on hypercalciuria and subsequent nephrocalcinosis.[10] Use of indomethacin in a pregnant woman with a suspected fetus with Bartter syndrome has many hazards to the fetus, such as negative effects on the ductus-arteriosus and the developing kidney, and no benefit for intrauterine control of the disease, since there is no hyperprostaglandinism in the unborn fetus.[2] It must be emphasized that indomethacin does not correct the primary chloride reabsorption defect of the kidney. There is also a report of spontaneous recovery in a case of antenatal Bartter syndrome after a period of treatment.[81]

Treatment of Gitleman syndrome

Replacement therapy is the main treatment for Gitleman syndrome, which means magnesium supplementation throughout life. Administration of magnesium in the form of $MgCl_2$ partially corrects hypomagnesaemia and hence prevents the appearance of tetany as well as compensating for ongoing chloride losses by the kidney.[4] Acid-base status, urinary Ca excretion and renin-angiotensin axis are all corrected. Also correction of hypokalaemia may occasionally require the addition of potassium salts and/or anti-aldosterone drugs such as spironolactone or amiloride.[86]

Treatment of classical Bartter syndrome

The primary aim of the treatment of this phenotype of Bartter syndrome is correction of hypokalaemia and alkalosis. Therefore administration of potassium chloride is always necessary. The dose of KCl supplementation should individually be titrated in accordance to the patient's needs and must balance the amount lost by the kidney. However, this mode of supplementation therapy is almost totally ineffective by itself, since administered potassium is lost through the kidney in a short period of time.[4]

It may seem logical that potassium-sparing agents such as spironolactone or triamterine would be an effective additive to supplementation therapy at this stage. Indeed these groups of medication offer an effective but transient control of hypokalaemia.[4] Addition of beta-adrenergic inhibitors, such as propranolol, is of no extra benefit. The most beneficial group of medication in treatment of classical Bartter syndrome is the prostaglandin synthetase inhibitors. Indomethacin (2–5 mg/kg/day), acetylsalicylic acid

(100 mg/kg/day), and ibuprofen (30 mg/kg/day) have all been tried. But the most frequently used is indomethacin. This medication is remarkably well tolerated by children. The initial response to indomethacin is remarkable, with correction of hypokalaemia, decrease of polyuria and reinstitution of weight gain. However, administration of indomethacin is an adjunct to potassium chloride therapy. Occasionally a patient may present with an additional problem of hypomagnesaemia requiring the addition of magnesium salts to the therapeutic regimen, as potassium wasting can be exaggerated by magnesium deficiency.[4] With long-term use of indomethacin one may occasionally encounter the reappearance of hypokalaemia and hyperreninaemia, requiring the readjustment of the dose of indomethacin. In adults, the use of angiotensin-converting-enzyme inhibitors (captopril, enalapril) has had conflicting results.[4,84] Their use in children, due to lack of data, requires caution with the risk of development of symptomatic hypotension.[4] Anaesthesia in patients with Bartter syndrome requires special attention with respect to maintaining of cardiovascular stability, control of plasma potassium level and the prevention of renal damage.[85]

Treatment of pseudo-Bartter syndrome

Hypokalaemic metabolic alkalosis, encountered in a variety of diseases without renal tubular pathology, will ultimately be corrected once the underlying disease has been identified and treated.[75] Any corrective fluid and electrolyte supplementation will therefore be a part of the treatment of the basic disease.

Conclusions

A clear understanding of the pathophysiology of different phenotypes of Bartter syndrome, including their genetic basis as well as the natural course and presentation from intra-uterine life to adulthood, plays the most crucial role in selecting the mode of therapy and management. It is only then that the appropriate management of an infant born with this disease can be instituted. In addition, long-term side-effects such as growth failure, tetany, nephrocalcinosis and renal failure may be prevented or treated.

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